Associations of Dehydroepiandrosterone Sulfate With Cardiometabolic Risk Factors in Prepubertal Children

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Context: Premature adrenarche (PA) has been associated with overweight and insulin resistance, but the associations of serum dehydroepiandrosterone sulfate (DHEAS) concentration with other cardiometabolic risk factors are uncertain.

Objective: To examine the associations of serum DHEAS concentration with several cardiometabolic risk factors in children.

Design: Cross-sectional data from the Physical Activity and Nutrition in Children Study.

Participants: Population sample of 207 girls and 225 boys aged 7.6 ± 0.4 years.

Main Outcome Measures: Cardiometabolic risk factors by serum DHEAS concentration.

Results: DHEAS correlated positively with body mass index standard deviation score, body fat percentage, lean body mass, high-sensitivity C-reactive protein (hs-CRP), and alanine aminotransferase (ALT) when adjusted for age and sex. The associations of DHEAS with hs-CRP and ALT disappeared when adjusted also for body fat percentage. When further adjusted for birth weight SD score, DHEAS correlated negatively with low-density lipoprotein (LDL) cholesterol and LDL/high-density lipoprotein (HDL) cholesterol ratio. LDL cholesterol was lower in children with DHEAS ≥40 μg/dL than in those with DHEAS <40 μg/dL, adjusted for age, sex, and body fat percentage (86.5 vs 92.3 mg/dL, $P = 0.029$). This association strengthened after further adjustment for birth weight SD score (85.3 vs 92.3 mg/dL, $P = 0.012$).

Conclusion: Higher DHEAS is not associated with an increased cardiometabolic risk in prepubertal children. Instead, it may be protective, evidenced by an association with lower LDL cholesterol and LDL/HDL cholesterol ratio. The increased cardiometabolic risk in PA shown in many studies may be due to low birth weight and childhood overweight associated with PA. (***J Clin Endocrinol Metab*** **103: 2592–2600, 2018)**

Adrenarche refers to the physiological increase of the production of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) from the adrenal gland that is typically detected at the age of 5 to 8 years (1, 2). Premature adrenarche (PA) is a variation of sexual maturation in mid-childhood that is characterized by elevated

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Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CV, coefficient of variation; DHEAS, dehydroepiandrosterone sulfate; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PA, premature adrenarche; PANIC, Physical Activity and Nutrition in Children; TC, total cholesterol; TG, triglyceride; VLDL, very low-density lipoprotein.

serum DHEAS concentrations for age and clinical signs of androgen action occurring before the age of 8 years in girls and 9 years in boys (2). PA and elevated serum DHEAS concentrations have been associated with low birth weight, rapid early growth (3–5), and increased adiposity in childhood and adolescence (2, 6, 7). Insulin resistance is a common finding in PA (8–10), and therefore children with PA may be at increased risk for the metabolic syndrome, type 2 diabetes, and cardiovascular disease in adulthood.

In some studies, PA has been related to increased plasma levels of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and LDL/high-density lipoprotein (HDL) cholesterol ratio (11–13). In a recent Turkish study among nonobese children, plasma triglyceride (TG) concentrations were higher in children with PA than in those without it (14). However, Finnish prepubertal girls with PA had similar serum lipid concentrations to age-matched control girls (10). Two studies have also reported higher blood pressure values in children with PA than in control subjects (11, 12). Moreover, higher serum DHEAS levels were associated with higher blood pressure in one study among black adolescents (15). To our knowledge, there are no studies on the associations of PA or serum DHEAS with plasma high-sensitivity C-reactive protein (hs-CRP) and alanine aminotransferase (ALT) in children, although these metabolic markers have been associated with childhood obesity and metabolic syndrome (16, 17).

The results of some studies suggest that PA is associated with an increased risk for the clustering of cardiometabolic risk factors (10, 12). In a German study among obese adolescent girls, serum DHEAS correlated positively with blood pressure, 2-hour plasma glucose in an oral glucose tolerance test, and plasma TG and uric acid (18). Serum DHEAS levels were also higher in girls with the metabolic syndrome compared with girls without it (18). However, children with PA had a similar prevalence of the metabolic syndrome compared with those without PA in a US study (19). In a Finnish study, the increased prevalence of the metabolic syndrome in children with PA was mainly explained by overweight and hyperinsulinemia (10).

The associations of serum DHEAS concentration with cardiometabolic risk factors in children are uncertain. We therefore investigated the associations of serum DHEAS concentration with measures of body composition, insulin resistance, glucose metabolism, lipid metabolism, systemic low-grade inflammation, and blood pressure in a general population of prepubertal children.

Subjects and Methods

Subjects

This study is part of the Physical Activity and Nutrition in Children (PANIC) Study, which is an ongoing controlled physical activity and dietary intervention study in a population sample of primary school children in the city of Kuopio, Finland (20). A total of 736 children aged 6 to 8 years were invited to participate in the study, and 512 of them (70%) participated in the baseline examinations in 2007 to 2009. The exclusion criteria for the current study were central puberty (defined as palpable breast tissue in girls and testicular volume ≥4 mL in boys) and any long-term medication having potential effects on growth or adrenal function, including inhaled corticosteroids. Data on variables needed for the analyses were available for 432 children (207 girls, 225 boys) who were included in the final study population. These children did not differ in sex distribution, age, or body mass index (BMI) SD score from the 80 children who were excluded. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo. All children and their parents gave informed written consent.

Assessments and analytical methods

A specially trained physician evaluated the clinical signs of androgen action (acne or comedones, adult-type body odor, oily hair, and pubic or axillary hair). PA was defined as the appearance of one or more clinical signs of androgen action before the age of 8 years in girls and 9 years in boys together with serum DHEAS concentration ≥40 μg/dL (21). Body height was measured three times with the child being in the Frankfurt plane without shoes using a wall-mounted stadiometer to an accuracy of 0.1 cm. The mean of the nearest two values was used in the analyses. Body weight was measured twice with the child having fasted overnight, having emptied the bladder, and standing in light underwear by a calibrated InBody 720® bioelectrical impedance device (Biospace Co. Ltd., Seoul, South Korea) to an accuracy of 0.1 kg. The mean of the two values was used in the analyses. Height SD score and BMI SD score were calculated according to Finnish growth reference data (22). Waist circumference was measured with an unstretchable measuring tape three times after expiration at middistance between the bottom of the rib cage and the top of the iliac crest. The mean of the nearest two values was used in the analyses. Blood pressure was measured manually using a calibrated Heine Gamma G7® aneroid sphygmomanometer (Heine Gamma G7, Herrsching, Germany) three times at 2-minute intervals from the right arm in the sitting position after a 5-minute rest. The mean of three measurements was used in the analyses. Body fat percentage and lean body mass were measured with the child having emptied the bladder and lying in light clothing by the Lunar® dual-energy X-ray absorptiometry device (Lunar Prodigy Advance; GE Medical Systems, Madison, WI). Birth length and birth weight were obtained from the registers of Kuopio University Hospital. Birth weight SD score was calculated according to Finnish growth reference data (23).

Venous blood samples were drawn in the morning after a 12-hour fast. Serum DHEAS concentration was determined using an ELISA kit (Alpha Diagnostic International, San Antonio, TX). The intra-assay coefficient of variation (CV) of our DHEAS assay was 7.5% to 11.5%, and the interassay CV was 7.0% to 11.0%. The detection limit of the assay was 0.52 μg/dL. Plasma glucose concentration was analyzed by the hexokinase method (Roche Diagnostics Co., Mannheim, Germany). Serum insulin concentration was analyzed using an electrochemiluminescence immunoassay with a sandwich principle (Roche Diagnostics Co.). Homeostatic Model

Assessment for Insulin Resistance (HOMA-IR) was calculated as a product of the plasma glucose (mg/dL) and serum insulin (μU/mL) divided by 405 (24). Plasma TC and TG concentrations were analyzed by colorimetric enzymatic assays (Roche Diagnostics Co.). Plasma HDL cholesterol and LDL cholesterol concentrations were analyzed using homogenous enzymatic colorimetric assays (Roche Diagnostics Co). Very low-density lipoprotein (VLDL) was separated by ultracentrifugation. Cholesterol concentration in the VLDL fraction and TG concentrations in VLDL and HDL fractions were determined with enzymatic colorimetric methods using commercial kits (Konelab System Reagents; Thermo Fisher Scientific, Vantaa, Finland) with an automated Konelab 20 XTi® analyzer (Thermo Fisher Scientific).

Plasma hs-CRP was measured using an enhanced immunoturbidimetric assay with a CRP (Latex) High Sensitive Assay reagent (Roche Diagnostics Co). hs-CRP values >10 mg/L were excluded from the analyses. A kinetic method according to the International Federation of Clinical Chemistry was used to analyze plasma ALT (Roche Diagnostic Co.). Plasma uric acid was measured using an enzymatic colorimetric test (Roche Diagnostics Co.). The intra-assay CV of all other measurements than DHEAS was 0.5% to 4.3%, and the interassay CV of these measurements was 1.2% to 5.1%.

The cardiometabolic risk score was calculated as a sum of *Z*-scores of variables in this study sample adjusted for age and sex using the following formula: waist circumference + the mean of systolic and diastolic blood pressure + serum insulin + plasma glucose + plasma TG − plasma HDL cholesterol (25). A higher cardiometabolic risk score indicated a less favorable cardiometabolic profile.

Statistical methods

SPSS statistical analysis software (Version 21.0; IBM Corp., Armonk, NY) was used for statistical analyses. We used a natural logarithmic transformation to normalize the skewed distributions of variables when needed. We compared clinical characteristics between sexes by *t* test for independent samples. We studied the correlation between DHEAS and birth weight SD score using Spearman rank order correlation test. We analyzed the correlations of DHEAS with BMI SD score and the cardiometabolic risk score using the Pearson correlation test and the partial correlation test adjusted for birth weight SD score. We studied the correlations of DHEAS with body fat percentage, lean body mass, and waist/height ratio using the partial correlation test adjusted for age and sex and for birth weight SD score in girls, boys, and all children combined. We analyzed the correlations of DHEAS with cardiometabolic risk factors (glucose, insulin, HOMA-IR, TC, LDL cholesterol, HDL cholesterol, LDL/HDL cholesterol ratio, VLDL cholesterol, TG, VLDL TG, HDL TG, systolic blood pressure, diastolic blood pressure, ALT, hs-CRP, and uric acid) using the partial correlation test adjusted for age and sex (Model 1) and for body fat percentage (Model 2) and birth weight SD score (Model 3) in girls, boys, and all children combined. We further analyzed the correlation between DHEAS and blood pressure using the partial correlation test adjusted for age and height SD score in both sexes. We studied differences in cardiometabolic risk factors and the cardiometabolic risk score between 369 children with lower DHEAS levels and 63 children with higher DHEAS levels [≥40 μg/dL, ≥1.08 μmol/L; a cut-off for biochemical adrenarche (21)] and between 417 children without PA and 15 children with PA using the general linear model adjusted for age and sex (Model 1) and for body fat percentage (Model 2) and birth weight SD score (Model 3). Associations or differences with $P < 0.05$ were considered statistically significant.

Results

Clinical characteristics

The boys were taller and heavier; had a lower body fat percentage, higher lean body mass, higher fasting plasma glucose levels, lower fasting serum insulin levels and HOMA-IR, higher plasma HDL cholesterol levels, lower LDL/HDL cholesterol ratio, and lower fasting plasma TG levels; and were longer and heavier at birth than the girls (Table 1).

Correlations of DHEAS with cardiometabolic risk factors

DHEAS correlated positively with BMI SD score (r = 0.193, $P < 0.001$) and negatively with birth weight SD score (r = −0.098, P = 0.043) without adjustments. The positive correlation between DHEAS and BMI SD score remained after adjustment for birth weight SD score (r = 0.225, $P < 0.001$). DHEAS correlated positively with body fat percentage (r = 0.181, $P < 0.001$) and lean body mass (r = 0.173, $P < 0.001$) when adjusted for age and sex. DHEAS also correlated positively with body fat percentage (r = 0.196, $P < 0.001$) and lean body mass (r = 0.230, $P < 0.001$) after additional adjustment for birth weight SD score. DHEAS correlated positively with waist-to-height ratio after adjustment for age, sex, and birth weight SD score (r = 0.106, P = 0.030),

DHEAS correlated negatively with LDL cholesterol after adjustment for age, sex, body fat percentage, and birth weight SD score (Table 2, Model 3) and with LDL/HDL cholesterol ratio adjusted for age, sex, body fat percentage (Table 2, Model 2), and birth weight SD score (Table 2, Model 3). DHEAS also correlated positively with ALT and hs-CRP adjusted for age and sex (Table 2, Model 1). However, these correlations were no longer statistically significant after additional adjustment for body fat percentage (Table 2, Model 2). DHEAS had no statistically significant correlations with other cardiometabolic risk factors (Table 2). Moreover, DHEAS was not correlated with the cardiometabolic risk score adjusted for age and sex (r = 0.017, P = 0.721) or after additional adjustment for birth weight SD score (r = 0.023, P = 0.644).

Correlations of DHEAS with cardiometabolic risk factors in girls and boys

In girls, DHEAS correlated positively with lean body mass (r = 0.257, $P < 0.001$), ALT (r = 0.140, P = 0.045), and systolic blood pressure (r = 0.155, P = 0.026) adjusted for age. The correlation between DHEAS and ALT disappeared

Table 1. Subject Characteristics

	All Children (N = 432)	Girls (n = 207)	Boys (n = 225)	*P* Value[a]
Age, y	7.6 ± 0.4	7.6 ± 0.4	7.6 ± 0.4	NS
Body height, cm	128.7 ± 5.5	127.5 ± 5.7	129.7 ± 5.2	<0.001
Body height SD score[b]	0.13 ± 0.99	0.07 ± 0.97	0.19 ± 1.00	NS
Body weight, kg	26.7 ± 4.7	26.1 ± 4.7	27.3 ± 4.7	0.005
BMI SD score[b]	−0.21 ± 1.06	−0.24 ± 1.02	−0.18 ± 1.87	NS
Waist/height ratio	0.44 ± 0.04	0.44 ± 0.03	0.44 ± 0.04	NS
Body fat percentage	19.6 ± 7.8	21.8 ± 7.1	17.4 ± 7.8	<0.001
Lean body mass, kg	20.6 ± 2.4	19.4 ± 2.1	21.7 ± 2.2	<0.001
Birth length, cm	50.0 ± 2.1	49.5 ± 2.1	50.4 ± 2.0	<0.001
Birth weight, g	3543 ± 531	3475 ± 536	3605 ± 521	0.011
Birth weight SD score[c]	−0.05 ± 1.0	0.01 ± 1.0	−0.10 ± 1.0	NS
GA at birth, wk	39.3 ± 1.5	39.2 ± 1.6	39.4 ± 1.4	NS
DHEAS, μg/dL	25.2 ± 21.9	24.4 ± 17.0	25.9 ± 25.6	NS
Glucose, mg/dL	86.7 ± 6.5	85.6 ± 6.9	87.6 ± 6.1	0.001
Insulin, μU/mL	4.5 ± 2.4	4.7 ± 2.3	4.2 ± 2.4	0.010
HOMA-IR	0.97 ± 0.56	1.01 ± 0.54	0.93 ± 0.58	0.044
TC, mg/dL	165.3 ± 23.1	166.4 ± 23.6	164.1 ± 23.2	NS
LDL-C, mg/dL	91.5 ± 19.3	93.4 ± 20.1	89.6 ± 18.5	NS
HDL-C, mg/dL	62.2 ± 12.0	60.6 ± 11.6	63.3 ± 12.0	0.023
LDL-C/HDL-C ratio	1.53 ± 0.47	1.61 ± 0.51	1.47 ± 0.43	0.005
VLDL-C, mg/dL[d]	4.63 ± 3.86	5.03 ± 4.25	4.63 ± 3.47	NS
TG, mg/dL	53.1 ± 22.1	54.9 ± 23.0	51.3 ± 21.2	0.048
VLDL TG, mg/dL[d]	24.8 ± 17.7	25.7 ± 15.6	23.9 ± 16.8	NS
HDL TG, mg/dL[d]	13.8 ± 3.5	14.0 ± 3.7	13.5 ± 3.3	NS
SBP, mm Hg	100 ± 7	100 ± 7	100 ± 7	NS
DBP, mm Hg	62 ± 7	62 ± 7	62 ± 7	NS
Cardiometabolic risk score	−0.05 ± 3.53	−0.17 ± 3.45	0.06 ± 3.61	NS
ALT, U/L	18.5 ± 5.8	18.1 ± 5.3	19.0 ± 6.1	NS
hS-CRP, mg/L	0.62 ± 0.92	0.62 ± 0.78	0.62 ± 1.03	NS
Uric acid, mg/dL	3.38 ± 0.64	3.44 ± 0.66	3.23 ± 0.62	NS

Values are means and standard deviations.

Abbreviations: C, cholesterol; DBP, diastolic blood pressure; GA, gestational age; NS, nonsignificant; SBP, systolic blood pressure.

[a]Data are from *t* test for independent samples.

[b]Body height SD score and BMI SD score based on Finnish references (22).

[c]Birth weight SD score based on Finnish references (23).

[d]Total number varies from 369 to 375 and from 169 to 172 in girls and from 200 to 203 in boys.

after further adjustment for body fat percentage ($r = 0.100$, $P = 0.161$), and the positive correlation between DHEAS and systolic blood pressure was no longer statistically significant after further adjustment for height SD score ($r = 0.094$, $P = 0.181$). DHEAS correlated negatively with LDL/HDL cholesterol ratio ($r = -0.148$, $P = 0.040$), VLDL cholesterol ($r = -0.193$, $P = 0.015$), TG ($r = -0.147$ $P = 0.041$), and VLDL TG ($r = -0.188$, $P = 0.018$) in girls after adjustment for age, body fat percentage, and birth weight SD score. In boys, DHEAS correlated positively with hs-CRP adjusted for age ($r = 0.167$, $P = 0.013$) but not after further adjustment for body fat percentage ($r = 0.094$, $P = 0.172$). DHEAS had no statistically significant correlations with other cardiometabolic risk factors in boys.

Differences in cardiometabolic risk factors between higher and lower DHEAS groups

BMI SD score was higher in children with higher DHEAS [mean, 0.11; 95% CI, −0.15 to 0.38] than in those with lower DHEAS (mean, −0.26; 95% CI, −0.37 to −0.15) after adjustment for birth weight SD score ($P = 0.011$). Lean body mass was higher in children with higher DHEAS (mean, 21.4 kg; 95% CI, 20.9 to 21.9 kg) than in those with lower DHEAS (mean, 20.5 kg; 95% CI, 20.2 to 20.7 kg) after adjustment for age and sex ($P = 0.001$). The difference in lean body mass between children with higher DHEAS (mean 21.7 kg; 95% CI, 21.2 to 22.1 kg) and those with lower DHEAS (mean, 20.4 kg; 95% CI, 20.2 to 20.6 kg) increased after adjustment for birth weight SD score ($P < 0.001$). The differences in BMI SD score and lean body mass between children with higher DHEAS and those with lower DHEAS were similar in girls and boys (P for interaction >0.05).

LDL cholesterol was lower in children with higher DHEAS than in those with lower DHEAS adjusted for age, sex, and body fat percentage (Table 3, Model 2). This difference increased after further adjustment for birth weight SD score (Table 3, Model 3). Children with higher

Table 2. Correlations Between Serum DHEAS Concentration and Cardiometabolic Risk Factors and Markers of Inflammation

	Model 1 (DHEAS, μg/dL), *r* (*P*)	Model 2 (DHEAS μg/dL), *r* (*P*)	Model 3 (DHEAS, μg/dL), *r* (*P*)
Glucose, mg/dL	−0.029 (0.553)	−0.049 (0.324)	−0.052 (0.297)
Insulin μU/mL	0.008 (0.871)	−0.052 (0.291)	−0.051 (0.308)
HOMA-IR	0.004 (0.937)	−0.054 (0.274)	−0.053 (0.286)
TC, mg/dL	−0.043 (0.379)	−0.052 (0.291)	−0.067 (0.177)
LDL-C, mg/dL	−0.066 (0.175)	−0.086 (0.082)	−0.101 (0.042)[a]
HDL-C, mg/dL	0.044 (0.364)	0.084 (0.089)	0.076 (0.128)
LDL-C/HDL-C ratio	−0.074 (0.127)	−0.114 (0.020)[a]	−0.120 (0.016)[a]
VLDL-C, mg/dL	−0.057 (0.270)	−0.069 (0.195)	−0.080 (0.136)
TG, mg/dL	−0.050 (0.304)	−0.070 (0.154)	−0.091 (0.068)
VLDL TG, mg/dL	−0.043 (0.410)	−0.068 (0.918)	−0.089 (0.096)
HDL TG, mg/dL	0.038 (0.472)	0.078 (0.141)	0.059 (0.275)
SBP, mm Hg	0.078 (0.105)	0.029 (0.562)	0.070 (0.168)
DBP, mm Hg	0.001 (0.982)	−0.040 (0.419)	−0.046 (0.356)
ALT, U/L	0.105 (0.029)[a]	0.086 (0.086)	0.088 (0.076)
hS-CRP, mg/L	0.128 (0.008)[a]	0.068 (0.138)	0.027 (0.584)
Uric acid, mg/dL	0.094 (0.053)	0.050 (0.313)	0.036 (0.467)

Analyzed by partial correlation test adjusted for age and sex (Model 1); adjusted for age, sex, and body fat percentage (Model 2); and adjusted for age, sex, body fat percentage, and birth weight SD score (Model 3).

Abbreviations: C, cholesterol; DBP, diastolic blood pressure; *r*, correlation coefficient; SBP, systolic blood pressure.

[a] $P < 0.05$.

DHEAS had also lower LDL/HDL cholesterol ratio than those with lower DHEAS adjusted for age and sex (Table 3, Model 1) and after additional adjustment for body fat percentage (Table 3, Model 2). This difference increased after further adjustment for birth weight SD score (Table 3, Model 3). The differences in LDL cholesterol and LDL/HDL cholesterol ratio between children with higher DHEAS and those with lower DHEAS were similar in girls and boys (*P* for interaction >0.05).

Associations of PA with cardiometabolic risk factors

TC was lower in 15 children with PA (mean, 152.5 mg/dL; 95% CI, 140.5 to 164.5), who represented 3.5% of all children, than in those without PA (mean, 166.0 mg/dL: 95% CI, 163.7 to 168.0) after adjustment for age and sex (*P* = 0.024) and further for body fat percentage (*P* = 0.013). This difference was similar after further adjustment for birth weight SD score (*P* = 0.004). LDL cholesterol was also lower in children with PA (mean, 78.11 mg/dL; 95% CI, 68.4 to 87.8) than in those without PA (mean, 92.0 mg/dL; 95% CI, 90.1 to 93.7) adjusted for age and sex (*P* = 0.05) and further for body fat percentage (*P* = 0.002). This difference remained after further adjustment for birth weight SD score (*P* = 0.001). Moreover, the LDL/HDL cholesterol ratio was lower in children with PA (mean, 1.22; 95% CI, 0.98 to 1.46) than in those without PA (mean, 1.55; 95% CI, 1.50 to 1.59) after adjustment for age and sex (*P* = 0.011) and further for body fat percentage (*P* = 0.002). This difference remained after additional adjustment for birth weight SD score (*P* = 0.002).

Discussion

Most previous studies on the associations of DHEAS with cardiometabolic risk factors in children have focused on premature pubarche or adrenarche. We studied whether serum DHEAS concentration is associated with cardiometabolic risk factors in a population sample of prepubertal children. Consistent with the results of a previous study (7), children with higher DHEAS had higher BMI SD score and body fat percentage than those with lower DHEAS. The most interesting finding of our study was the association of higher DHEAS with lower LDL cholesterol that persisted after controlling for sex, age, body fat percentage, and birth weight SD score. Furthermore, plasma LDL/HDL cholesterol ratio was lower in children with higher serum DHEAS than in those with lower DHEAS. A higher serum DHEAS concentration was also associated with higher plasma ALT and hs-CRP concentrations, but these associations disappeared after further adjustment for body fat percentage.

The observed associations of higher DHEAS with lower fasting LDL cholesterol and LDL/HDL cholesterol ratio in prepubertal children are consistent with the results of a Turkish study that showed a better lipid profile, such as lower LDL cholesterol and TG and higher HDL cholesterol, in prepubertal girls with PA born appropriate for gestational age compared with control girls (26). We found no association between DHEAS and HDL cholesterol, which is consistent with the observation of a previous Finnish study among children with PA (10). In a recent Chilean study, 7-year-old children with

Table 3. Cardiometabolic Risk Factors in Children With Lower and Higher DHEAS Levels

	Model 1, Adjusted for Age and Sex			Model 2, Adjusted for Age, Sex, and Body Fat Percentage			Model 3, Adjusted for Age, Sex, Body Fat Percentage, and Birth Weight SD Score		
	DHEAS <40 μg/dL, Mean (95% CI), n = 314–369[a]	DHEAS ≥40 μg/dL, Mean (95% CI), n = 55–63[a]	*P*	DHEAS <40 μg/dL, Mean (95% CI), n = 303–356[a]	DHEAS ≥40 μg/dL, Mean (95% CI), n = 53–61[a]	*P*	DHEAS <40 μg/dL, Mean (95% CI), n = 297–362[a]	DHEAS ≥40 μg/dL, Mean (95% CI), n = 51–61[a]	*P*
Glucose, mg/dL	86.5 (86.0–87.2)	86.7 (85.1–88.3)	0.882	86.7 (86.0–87.4)	86.7 (85.1–88.3)	0.898	86.7 (86.0–87.4)	86.7 (85.1–88.5)	0.927
Insulin, μU/mL	4.4 (4.2–4.7)	4.7 (4.1–5.3)	0.372	4.5 (4.3–4.7)	4.6 (4.0–5.1)	0.655	4.5 (4.3–4.7)	4.6 (4.0–5.1)	0.700
HOMA-IR	0.97 (0.91–1.02)	1.03 (0.89–1.16)	0.399	0.98 (0.93–1.03)	1.00 (0.86–1.13)	0.680	0.99 (0.93–1.04)	0.99 (0.86–1.13)	0.715
TC, mg/dL	165.3 (163.7–168.3)	162.2 (156.4–168.0)	0.263	166.0 (163.7–168.7)	161.8 (156.0–168.0)	0.224	166.4 (163.7–168.7)	161.0 (154.8–166.8)	0.127
LDL-C, mg/dL	92.3 (90.4–94.2)	87.3 (82.2–92.0)	0.061	92.3 (90.4–94.2)	86.5 (81.5–91.1)	0.029[b]	92.3 (90.4–94.2)	85.3 (80.7–90.4)	0.012[b]
HDL-C, mg/dL	61.8 (60.6–62.9)	63.3 (60.6–66.4)	0.232	61.8 (60.6–62.9)	64.1 (61.0–67.2)	0.120	61.8 (60.6–62.9)	64.1 (61.0–66.8)	0.153
LDL-C/HDL-C ratio	1.6 (1.5–1.6)	1.4 (1.3–1.6)	0.029[b]	1.6 (1.5–1.6)	1.4 (1.3–1.5)	0.008[b]	1.6 (1.5–1.6)	1.4 (1.3–1.5)	0.005[b]
VLDL-C, mg/dL	5.0 (4.2–5.4)	4.2 (3.5–5.4)	0.227	5.0 (4.2–5.4)	4.2 (3.5–5.4)	0.286	5.0 (4.6–5.4)	4.4 (3.1–5.4)	0.133
TG, mg/dL	53.1 (51.3–55.8)	52.1 (46.9–57.5)	0.602	54.0 (51.3–55.8)	52.2 (46.0–57.5)	0.583	54.0 (51.3–56.6)	50.4 (45.1–56.6)	0.356
VLDL TG, mg/dL	24.8 (23.0–27.4)	24.8 (19.5–29.2)	0.594	25.7 (23.0–27.4)	23.9 (19.5–29.2)	0.581	25.7(23.9–27.4)	23.0 (18.6–28.3)	0.273
HDL TG, mg/dL	13.9 (13.5–14.3)	13.4 (12.4–14.3)	0.213	13.9 (13.5–13.3)	13.5 (12.7–14.5)	0.405	13.8 (13.5–14.2)	13.8 (13.5–14.2)	0.293
SBP, mm Hg	100 (99–101)	101 (99–102)	0.581	100 (99–101)	100 (99–100)	0.863	100 (99–101)	100 (98–102)	0.890
DBP, mm Hg	62 (61–62)	61 (59–63)	0.350	62 (61–62)	61 (59–62)	0.249	62 (61–62)	60 (58–62)	0.142
ALT, U/L	18.4 (17.8–19.0)	19.3 (17.9–20,8)	0.123	18.4 (17.8–19.0)	19.2 (17.8–20.7)	0.183	18.5 (17.9–19.0)	19.3 (17.8–20.8)	0.140
hS-CRP, mg/L	0.60 (0.50–0.69)	0.74 (0.51–0.97)	0.073	0.60 (0.51–0.70)	0.73 (0.49–0.96)	0.107	0.61 (0.51–0.70)	0.73 (0.45–0.97)	0.123
Uric acid, mg/dL	3.35 (3.29–3.42)	3.56 (3.40–3.71)	0.061	3.36 (3.30–3.43)	3.53 (3.37–3.69)	0.129	3.36 (3.30–3.43)	3.51 (3.35–3.67)	0.186

Analyzed by general linear model. *P* values are for logarithmically transformed variables, but adjusted means and 95% CIs are presented in original units.

Abbreviations: C, cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]The number of children in Models 1–3 is variable because HDL TG, VLDL-C, and VLDL TG were not available for all children.

[b]$P < 0.05$.

normal birth weight and DHEAS >75th percentile of the sample had higher HDL cholesterol than their counterparts adjusted for sex and age, but there was no difference in total or LDL cholesterol or TG between these groups (27). In some other studies, adverse lipid profiles have been reported in children with increased DHEAS, but birth weight and current weight have not been controlled for in the analyses (11, 12, 14). Furthermore, reduced prenatal growth was found to be associated with dyslipidemia in a Spanish study among girls with premature pubarche or a history of it (28). One explanation for the differences between our observations and those of previous studies may be that only few children in the present population-based sample had low birth weight, and we adjusted all data for current body fat percentage.

Similar to our findings in prepubertal children, some studies in adults have shown that DHEA and DHEAS are negatively associated with total and LDL cholesterol (29). Moreover, a 4-week exogenous DHEA treatment decreased total and LDL cholesterol in men (30). However, clinical trials have failed to show an effect of DHEA treatment on serum lipids in elderly women (31, 32). Thus, although DHEA and DHEAS have been considered as antiatherogenic steroids in some studies among adults, the issue is not clear, and there is evidence for and against this conclusion (33).

We found that higher DHEAS was associated with higher lean body mass in prepubertal children, which is consistent with the results of previous studies in children (34, 35). We suggest that the inverse associations of DHEAS with LDL cholesterol and LDL/HDL cholesterol ratio in the current study are partly due to higher skeletal muscle mass in children with higher serum DHEAS concentrations. Exercise training has increased lean body mass and improved lipid profile in some studies among adults (36), but data on the association between lean body mass and lipid profile in children are scarce. DHEAS has also been found to accelerate sexual maturation (2, 37, 38), which has been observed to decrease TC, LDL cholesterol, and HDL cholesterol (39, 40).

DHEAS is converted to more potent androgens, such as testosterone and DHT, and to estradiol in peripheral tissues. Sex steroids regulate the activity of lipolytic enzymes (41, 42) and can thereby influence lipid metabolism. Androgens increase and estrogens suppress plasma hepatic lipase activity, whereas lipoprotein lipase activity regulated by sex steroids can be attributed to changes in hepatic lipase activity (41). The observed inverse associations of DHEAS with plasma LDL cholesterol and LDL/HDL cholesterol ratio may be partly explained by the complex effects of sex steroids on hepatic lipase activity.

We found some differences in the associations of DHEAS with cardiometabolic risk factors between sexes. DHEAS correlated negatively with LDL/HDL cholesterol ratio, VLDL cholesterol, TG, and VLDL TG after controlling for age, body fat percentage, and birth weight SD score in girls but not in boys. One reason for these observations could be that the peripheral conversion of DHEAS to more potent androgens and further to estrogens is more efficient, and thus the beneficial effects of DHEAS on metabolism are stronger in girls than in boys (43). The associations of sex steroids with cardiometabolic risk factors and their differences between sexes may be further clarified by developing and using more sensitive sex steroid assays.

In our study among prepubertal children, DHEAS was not associated with fasting glucose, insulin, or HOMA-IR, which is in agreement with the results of previous studies among children (7, 44). Insulin resistance increases by age together with IGF-1 and particularly so in puberty (44). Moreover, children with PA often have insulin resistance (2, 8–10). However, DHEA and DHEAS have been found to have insulin-sensitizing effects in adults (45, 46). DHEA replacement was also observed to reduce abdominal fat and improve insulin sensitivity in a randomized controlled trial among elderly people (46). Moreover, DHEA and DHEAS have been inversely associated with fasting glucose and insulin in nondiabetic men (47) and with the risk of type 2 diabetes in middle-aged and elderly men and women (48). Our findings suggest that higher DHEAS is not associated with hyperinsulinemia in children with normal birth weight and childhood body weight, although insulin resistance is common among children with PA (2, 8–10).

DHEAS correlated positively with systolic blood pressure among girls in the current study, but the association was explained by height. Moreover, there was no difference in systolic and diastolic blood pressure between children with higher DHEAS and those with lower DHEAS and between children with PA and those without it. Consistent with our findings, systolic and diastolic blood pressure adjusted for weight and height was similar in Finnish girls with PA and in control girls (10). Two studies have reported higher blood pressure in children with PA than in their healthy peers, but height was not taken into account in the analyses (11, 12).

We found a positive correlation between DHEAS and hs-CRP in all children and in sex-specific analyses among boys. This association was explained by body fat content, as was the case with ALT. To our knowledge, there are no previous reports on the association of DHEAS with hs-CRP in children or in young healthy adults. However, total testosterone was inversely associated with hs-CRP in young adult men but not in women after adjustment for BMI, age, waist circumference, and smoking (49). Although the androgens may have a potential independent role in inflammatory processes, more research on these associations is needed, especially in healthy populations.

The strengths of the current study include a relatively large population sample of prepubertal children, the accurate measurement of body fat percentage, and the opportunity to take body fat percentage and birth weight SD score into account in the analyses. The weakness of this study is that we do not have data on estradiol or testosterone concentrations. However, even if measured, the concentrations of testosterone at this age would have been low, and concentrations of estradiol would have been undetectable in most children. Neither did we analyze sex hormone binding globulin concentrations. Furthermore, DHEAS was measured with an immunoassay, not with liquid chromatography-tandem mass spectrometry, but this is not a problem due to the abundance of DHEAS in relation to the potential cross-reacting steroids in our serum samples. Finally, we had limited statistical power for analyses dealing with PA due to the small number of children with PA.

We found positive correlations of serum DHEAS concentration with BMI SD score, body fat percentage, lean body mass, ALT, and hs-CRP but not with fasting glucose, fasting insulin, HOMA-IR, or the cardiometabolic risk score. However, we observed that a higher serum DHEAS concentration was associated with lower plasma LDL cholesterol and LDL/HDL cholesterol ratio after taking body fat content and birth weight into account. Our findings therefore indicate that DHEAS is metabolically neutral or even beneficial for plasma lipid profile and suggest that the unfavorable associations reported in previous studies are mostly explained by low birth weight or childhood overweight.

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